

STEM CELLS IN TRAUMATIC BRAIN INJURY

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ABSTRACT

Traumatic Brain Injury (TBI) is a devastating clinical condition that often causes permanent incapacity, especially in the younger population. The clinical relevance of TBI justifies the scientific interest in the pathophysiology of TBI, as well as in protective effects and development of treatment options. Stem cells have the ability to induce neuroprotection and neural repair inflammatory suppression, causing tissue reconstruction completely or partially damaged cells to preventing cell death to evolve. However the neurological improvement observed in preclinical studies and clinical tests based on neurological and behavioral disorders and the mechanism of action of stem cells remains unknown. In this study the authors discuss the current status of using stem cells to treat TBI, including the basic cell types and potential mechanisms of action, preclinical data and points out lack of studies and hurdles for clinical application. The authors also focusing on the recent demonstration that neurogenesis occurs in all mammals throughout adult life, although at a low rate, is possible to induce neurogenesis de novo in the adult mammalian brain, particularly in the neocortex where it does not normally occur and that it may become possible to manipulate endogenous multipotent precursors in situ to replace lost or damaged neurons. Elucidation of the relevant molecular controls may both allow control over transplanted precursor cells and potentially allow the development of neuronal replacement therapies for neurodegenerative disease and other central nervous system injuries that do not require transplantation of exogenous cells. Discuss strategies of enhance the neurogenesis (for example by exogenous tropic factor administration) and the transplantation of different types of neural progenitor cells after TBI. Each strategy is discussed with an emphasis on highlighting the progress and limiting factors relevant to the development of clinical trials of cellular replacement therapy for severe TBI in humans.

Keywords: Stem Cells, Traumatic Brain Injury, Adult Neurogenesis, Progenitor Migration

1. INTRODUCTION

Traumatic Brain Injury (TBI) is a devastating clinical condition that often causes permanent incapacity, particularly in the younger population. The clinical relevance of TBI justifies the scientific interest in the pathophysiology of TBI, protective effects and development of treatment options.

The extent of the neurologic deficits caused by lesions is determined by two main factors: The primary mechanical insult and the secondary insult caused by inflammation, compression and ischemia Cheng *et al.*, (2012). The primary lesion is caused by the trauma itself

and involves cellular death and tissue necrosis, independently of biological factors. The mechanisms underlying secondary lesions involve activation of inflammation, tissue ischemia, reperfusion deficits, edema, lipidic peroxidation, calcium influx and particularly apoptosis. These secondary lesions constitute the main target for the development of novel therapeutic approaches (Cheng *et al.*, 2012). Among these novel strategies, new neuroprotective agents are being developed, with researchers conducting trials on therapeutic agents such as levodopa/carbidopa as well as several neurotrophic factors. The efficacy of these drugs however, has yet to be confirmed. Other substances

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including cannabinoid dexamabinol, erythropoietin and gamaglutamylcysteine ethyl ester have demonstrated neuroprotective effects in humans at an experimental stage, where their administration might limit tissue damage and increase the potential for clinical recovery (Lok *et al.*, 2011).

Stem cells have the ability to induce neuroprotection, inflammatory suppression and neural repair, allowing reconstruction of totally damaged tissues or preventing partially damaged cells from evolving to cell demise (Erceg and Stojkovic, 2009). However, the neurological improvements observed in pre-clinical and clinical trials have been based on results of neurological and behavioral tests, while the underlying mechanism of action of stem cells remains unknown. The percentage of stem cells able to differentiate into neurons is believed to be negligible or even non-existent, with improvements seen in pre-clinical and clinical trials attributable to the secretion of trophic factors triggering endogenous repair mechanisms (Heile and Blinker, 2011; Yang *et al.*, 2012). In addition, tentative pre-clinical data reveals obstacles in the interpretation and translation of the preliminary potential for treatment of TBI in humans.

1.1. Physiopathology of TBI

While knowledge on stem cells has advanced in recent years, knowledge on the physiopathology of TBI has lagged, severely hampering the search for an effective stem cell-based therapy in TBI.

1.2. Primary Lesion

Primary lesion is caused by impact to the cortical and subcortical brain structures, causing focal or Diffuse Axonal Injury (DAI) and rupture of the Blood Brain Barrier (BBB) (Albert-Weibenberger *et al.*, 2012). The primary event is accompanied by a huge ionic influx known as traumatic depolarization. The main inflammatory neurotransmitters released are the excitatory aminoacids. This may explain the physiopathology of DAI in TBI. Brain edema caused by rupture of the BBB and swelling of astrocytes raises intracranial pressure (Kahle *et al.*, 2013). Vascular endothelial growth factor also plays a role in the rupture of neuronal tissue and increases permeability of the BBB through the synthesis and release of nitric oxide (Woodcock and Morganti-Kossmann, 2013).

1.3. Secondary Lesion

Secondary lesion is associated with the release of excitatory aminoacids, oxygen radicals and with the production of nitric oxide, leading to activation of N-Methyl-D-Aspartate (NMDA), 2-amino-3-propanoic acid

(5-methyl-3-oxo-1, 2-oxazol-4-yl) (AMPA), alpha-7 nicotinic receptor ($\alpha 7$), Nicotinic Acetylcholine Receptor (NACR) and calcium influx (Hinzman *et al.*, 2012; Kelso and Oestreich, 2012). This cascade of events promotes mitochondrial rupture and release of free radicals with tissue peroxidation. One theory holds that the release of excitatory aminoacids leads to calcium influx in neurons and other brain cells, promoting oxygen-free radical reactions. The increased calcium and presence of free radical molecules creates an unstable environment in which the cell can increase the production and release of nitric oxide and excitatory aminoacids (e.g., glutamate) (Oliva *et al.*, 2012; Hinzman *et al.*, 2012). Nitric oxide can participate in reactions of oxygen radicals and in lipid peroxidation among neighboring cells (Xiong *et al.*, 2009). Secondary lesions constitute the main target for the development of novel therapeutic approaches (Kumar and Loane, 2012) given they are the main determinant of morbidity and mortality in TBI. To date, several genes have been implicated for influencing outcome after TBI with APOE being the most extensively studied. The proposed mechanism by which Apolipoprotein E (APOE) affects the clinic pathological consequences of TBI is multifactorial and includes amyloid deposition, disruption of cytoskeleton stability, cholinergic dysfunction, oxidative stress, neuroprotection and central nervous system plasticity in response to injury. The Catechol-O-Methyltransferase (COMT) and Dopamine Receptor D2 (DRD2) genes have been less extensively studied and may influence dopamine dependent cognitive processes such as executive/frontal lobe functions. Inflammation, a prominent component in the path physiological cascade initiated by TBI, is in part mediated by the interleukin genes, while the apoptosis that occurs as a consequence of TBI may be modulated by polymorphisms of the p53 gene. The Angiotensin Converting Enzyme (ACE) gene may affect TBI outcome via mechanisms of cerebral blood flow and/or auto regulation whereas the calcium channel, voltage-dependent, P/Q type, alpha 1A subunit (CACNA1A) gene may exert an influence via the calcium channel and its effect on delayed cerebral edema. Although several potential genes that may influence outcome after TBI have been identified, future investigations are needed to validate these genetic studies and identify new genes that might influence outcome following TBI (Dardiotis *et al.*, 2012).

1.4. Therapeutic Application of Stem Cells in TBI

For therapeutic application, separate stem cells can be divided into adult or embryonic types, exogenous

or endogenous origin and local or systemic routes of administration.

1.5. Exogenous Embryonic Stem Cells (ESCs)

Embryonic Stem Cells are pluripotent cells capable of differentiating into any of the cell types. ESCs offer the advantage of allowing a large number of cells to be expanded in culture and can produce specific neuron types for transplantation (Leao *et al.*, 2010). This characteristic is relevant in that stem cell replacement therapies require a large number of cells. However, ESCs have the drawback of ethical and religious issues, are prone to rejection upon transplantation and can create teratomas when administered *in vivo* (Qu *et al.*, 2012).

Studies of transplantation of ESCs in animal models have shown good results. However, broader knowledge is needed before running these studies in humans (Abdullah *et al.*, 2012).

Classically, ESCs have been the most common source of Neural Stem Cells (NSCs), although recent studies have isolated NSCs from areas with active neurogenesis in the Subventricular Zona (SVZ) of the lateral ventricle of rats (Foti *et al.*, 2013).

1.6. Exogenous Adult Neural Stem Cells (NSCs)

NSCs are multipotent cells, i.e., have limited potential for differentiation into cells of other tissue types. NSCs can be identified by the immunocytochemical markers nestin, an intermediate filament (Cristini *et al.*, 2011), musashi 1, an RNA-binding protein (Reis and Hermanson, 2012) and the transcription factors Sox1 and Sox2 (Archer *et al.*, 2011). Nestin and musashi 1 are specific to neural progenitor cells and are not expressed in fully differentiated neurons.

In transplantation of NSCs into the cortex of rats submitted to TBI, 1-3% of cells became engrafted after 2 weeks of treatment. NSC engraftment and transdifferentiation was associated with an improvement in motor function, but no change in cognitive function was noted (Harting *et al.*, 2009). However, other authors of similar studies have found improved cognitive function in rats (Park *et al.*, 2012).

NSCs systemically infused 2h after TBI showed reduction in neurological decline, edema formation, inflammatory infiltration, apoptosis as well as attenuation of activity of Tumor Necrosis Factors alpha (TNF- α), Interleukin 6 (IL-6) and the transcription factor NF- κ B, compared to other treatment types (Lee *et al.*, 2008). Other authors suggested an optimal time point for transplant of 7-14 days post injury. At this juncture, the microenvironment of the lesion has low levels of cytokines (TNF, IL-1 α , IL-1 β and IL-6) where high

cytokine levels can have a neurotoxic action (Zhu *et al.*, 2006). Beyond this time window the glial scar forms a barrier enveloping the lesion site which inhibits the local blood circulation vital for graft survival (Bhalala *et al.*, 2012).

The fundamental challenges to successful translation of the large body of pre-clinical work into clinical practice involve the delivery of NSCs to the target location. Direct implantation and intrathecal, intravenous and intra-arterial infusion, has shown low engraftment rates and risk of distal emboli (in intravascular infusions). Novel delivery methods such as nanofiber scaffold implantation could provide the structural and nutritive support required for NSCs proliferation, engraftment and differentiation (Walker *et al.*, 2009).

1.7. Exogenous Induced Pluripotent Stem Cells (iPS)

Induced pluripotent cells hold great promise for their potential use in stem cell-based therapy. A number of authors believe the ectopic expression of 4 transcription factors (Oct4, Sox2, Myc and Klf4) was sufficient to reprogram the differentiation status of somatic cells to the pluripotent state of ESCs (Ramos-Mejia *et al.*, 2012). Breton *et al.* (2013) showed that the transduction of different positions of the pluripotency factors (e.g., Oct4, Sox2, Nanog and LIN28) can have a similar effect on reprogramming of cell lines in equines and humans for pluripotent cells that exhibit the essential features of ESCs. Thus, iPS has the advantage of being derived from the patient thereby precluding the risk of rejection.

Although promising, iPS has the drawbacks of low efficiency of reprogramming, risk of using viral infection in their production and formation of tumors after transplantation. Thus, there are several hurdles to overcome before iPS cells can be considered a potential patient-specific cell therapy (Orlacchio *et al.*, 2010).

1.8. Exogenous Mesenchymal Stem Cells (MSCs)

Mesenchymal Stem Cells are multipotent and first isolated from bone marrow. These cells can be administered intravenously or injected directly into the site of the brain lesion for a better outcome (Lam *et al.*, 2013). The action of MSCs involves the secretion of growth factors, exchange of genes and proteins through cell-to-cell fusion or contact (Kim *et al.*, 2010), induction of angiogenesis (Khalili *et al.*, 2012) and immunomodulation effects (Sarnowska *et al.*, 2009). The main advantages of using this cell type over other types transplanted cell (e.g., umbilical cord blood, mobilized peripheral blood and neural stem/progenitor cells) is their ease of obtention, potential for

autologous transplant, fast expansion *ex vivo*, immune privilege of allogeneic cells and ability to migrate to the site of inflammation (Uccelli *et al.*, 2006).

The factors secreted by MSCs include: (Glial Cell-Line Derived Neurotrophic Factor (GDNF), Brain-Derived Neurotrophic Factor (BDNF), Nerve Growth Factor (NGF), Vascular Endothelial Growth Factor (VEGF), among others (Rooney *et al.*, 2009; Tan *et al.*, 2011; Alder *et al.*, 2012). MSC cultures in supernatant from rat brain submitted to closed traumatic brain trauma also showed increased BDNF, NGF and VEGF, in addition to an increase in Hepatocyte Growth Factor (HGF) (Kim *et al.*, 2010). The large number of factors secreted can promote self-repair of residing tissue cells.

Several pre-clinical trials investigating the use of MSCs in TBI models have shown the migration of cells away from the lesion site and subsequent survival of MSCs, as well as their differentiation into neurons and astrocytes, leading to enhanced motor function (Wang *et al.*, 2012).

The considerable therapeutic potential of human multipotent Mesenchymal Stromal Cells has generated markedly increasing interest from a wide variety of biomedical disciplines. However, investigators report MSCs studies using different methods of isolation and expansion and different approaches to characterizing the cells. Thus, it is increasingly difficult to compare and contrast study outcomes, hindering progress in the field. To begin to address this issue, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy proposes minimal criteria to define human MSCs. First, MSCs must be plastic-adherent when maintained under standard culture conditions. Second, MSCs must express CD105, CD73 and CD90 and lack expression of CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA-DR surface molecules. Third, MSCs must differentiate into osteoblasts, adipocytes and chondroblasts *in vitro* (Vallone *et al.*, 2013).

Several publications have previously demonstrated that the intravenous delivery of MSCs after traumatic brain injury affords neuroprotection via interaction with splenocytes, leading to an increase in systemic anti-inflammatory cytokines. (Scheibe *et al.*, 2012; Walker *et al.*, 2010). MSCs have also been shown to differentiate *in vivo* and *in vitro*. Markers for human MSCs include: CD10, CD13, CD49b, CD49d, CDw90 and Flk1 (Montesinos *et al.*, 2009; Gong *et al.*, 2011).

The umbilical cord is an abundant source of hematopoietic stem cells. However, investigations reveal a subtype of cells from umbilical cord which do not express marking with CD45 (hematopoietic cell marker) and do not differentiate into hematopoietic cells *in vitro*. This fraction of mononuclear cells can be expanded in

culture and upon stimulation by basic Fibroblast Growth Factor (bFGF) and human epidermal growth factor (hEGF), differentiate into cells which mark positively for the neural markers beta-tubulin III and Glial Fibrillary Acidic Protein (GFAP) (Bicknese *et al.*, 2002).

Mononuclear stromal cells from umbilical cord have a substantial inflammatory, angiogenic effect and have exhibited engraftment rates of over 20% when transplanted into the Subventricular Zone (SVZ) of neonatal rats, making them attractive therapeutic agents (Walczak *et al.*, 2010).

1.9. Exogenous Adipose-Derived Stem Cells (ADSCs)

ADSCs represent a promising source of large quantities of stem cells (Xue *et al.*, 2010) found improvements in motor function (differentiation in neurons and oligodendrocytes) in a spinal cord injury model in rats after intravenous administration of ADSCs (Arboleda *et al.*, 2011).

Another study investigated whether transplantation of Schwann cells differentiated from Adipose-Derived Stem Cells (ADSC-SCs) of rats could promote functional improvement after contusion brain injury, with a focus on effects on reactive gliosis. ADSCs were isolated and expanded from groin adipose tissue of rats and then differentiated into Schwann cells. ADSC-SCs were transplanted into contused rat brain. Immunofluorescence and Western blotting were used to analyse reactive gliosis. In conclusion, transplantation of ADSC-SCs can effectively promote locomotor functional recovery and reduce reactive gliosis after contusion brain injury in rats. ADSCs represent a strong candidate for future research in cell therapies (Yang *et al.*, 2011).

1.10. Endogenous Stem Cell Therapy

Endogenous neurogenesis in adults was first described by (Luskin *et al.*, 1997) and later confirmed by other authors (Sawamoto *et al.*, 2011), who showed the presence of Neural Stem Progenitor Cells (NSPCs) within the Subventricular Zona (SVZ) of adult rats that migrated to the olfactory bulb and joined the neural network known as the Rostral Migratory Stream (RMS).

Normal adult brain has two different regions with continuous growth generating new neurons: the SVZ located proximal to the lateral ventricles and the granule cell layer and the Subgranular Zone (SGZ) of the dentate gyrus of the hippocampus (Patzke *et al.*, 2013). Evidence suggests that the adult brain has the potential for compensatory striatal neurogenesis, although the level of

this neurogenesis is insufficient to counter the progressive neuronal loss which takes place in a diseased or damaged adult brain. Consequently, therapeutic methods may be harnessed to boost neurogenesis and direct migration of progenitor cells towards those specific areas of the brain with neuronal loss.

The studies available indicate an increase in progenitor proliferation of the SVZ region in response to TBI. Other studies however, have found reduced progenitor proliferation in the SVZ region post-TBI, suggesting that the extent of damage in different lesions can result in commensurately different molecular responses both proximal to the lesion and also in the SVZ, giving rise to disparities in cell proliferation within the SVZ (Eriksson *et al.*, 1998).

Adult multipotent precursors are not limited to the olfactory epithelium, anterior SVZ and hippocampus of the adult mammalian brain, having been cultured *in vitro* from caudal portions of the SVZ, the septum, striatum, cortex, optic nerve, spinal cord and retina. This feature augments the efficacy potential of neuronal replacement therapies based on *in situ* manipulation of endogenous precursors (Emsley *et al.*, 2004).

Precursors derived from all these regions can self-renew and differentiate into neurons, astroglia and oligodendroglia *in vitro*. It is thought that they normally differentiate only into glia or die *in vivo*. Cells from each region have different requirements for proliferation and differentiation. For instance, precursors derived from septum, striatum, cortex and optic nerve have been reported to require FGF-2 to proliferate and differentiate into neurons *in vitro*.

Endogenous stimulation occurs mainly due to the release of growth factors such as EGF, FGF-2, bFGF, aFGF, BDNF, NGF, NT-3, VEGF, GDNF, IGF-1 and SDF-1 alpha (Li *et al.*, 2010). These growth factors can be administered by intraventricular, intraparenchymal or intrathecal injection. Some authors report that growth factors, besides improving proliferation, also promote increased migration and gliogenesis of Neural Precursor Cells (NPCs) (Sirko *et al.*, 2010). However, the exact physiopathological mechanisms of functional recovery remain unknown.

Endogenous stimulation has the advantages of avoiding any ethics problems (occurring with embryonic and fetal cells), being less invasive and having no rejection problems (present in exogenous NSPCs) (Saha *et al.*, 2012).

Several authors have described the CBP/p300-phosphorylated Smad complex. This CBP/p300-phosphorylated Smad complex, when bound to NSCs, can determine their differentiation. If the complex is

trapped with Signal Transducers and Activators of Transcription (STAT) phosphorylated 3, the NSCs differentiate into cells with astroglia lineage. Conversely, if the complex is bound with the proneural basic Helix-Loop-Helix (bHLH) factor, such as neurogenin 1 and 2, cells differentiate into a neuronal lineage (Herrera *et al.*, 2010). The Sox2 gene may also play a key role in neural differentiation (Lodato *et al.*, 2013).

Once the NSCs decide to differentiate into neuronal lineage, a cascade of hundreds of genes is regulated throughout neurogenesis to transform the immature neuron into its mature phenotype. Many of these neural genes are controlled by RE1-Silencing Transcription Factor (REST). REST acts as a repressor of neuronal genes in non-neural cells whereas REST regulation activates the large networks of genes required for neural differentiation (Dewald *et al.*, 2011).

Brain-Derived Neurotrophic Factor (BDNF) is also important in regulating the survival and destiny of progenitor cells in adult brain. Studies have been conducted comparing BDNF of healthy versus damaged brain in terms of the distribution of progenitor cells and levels of differentiation and survival. BDNF was overexpressed in the SVZ via recombinant Adeno-Associated Virus (AAV1/2) delivery and newly generated cells were identified using Bromodeoxyuridine (BrdU) labeling. Selective striatal cell loss was induced in a subgroup of rats by unilateral striatal injection of Quinolinic Acid (QA) 21 days after AAV1/2 injection. BDNF has been shown to promote both neuronal differentiation and the survival of newly generated daughter cells (Henry *et al.*, 2007; Kells and Connor, 2008). *In vivo*, BDNF delivery to SVZ-derived adult neural progenitor cells increased neuronal recruitment to the olfactory bulb (Tanaka *et al.*, 2010) and resulted in ectopic addition of newly generated neurons, expressing markers of γ -aminobutyric acid (GABA) ergic medium spiny striatal neurons, to the striatum of normal adult rat brain (Hou *et al.*, 2008). This evidence points to the conclusion that elevated levels of BDNF, induced by injury, can increase the recruitment of progenitor cells to the site of lesioned striatum and promote neuronal differentiation in both normal and damaged striatum. Increasing BDNF expression may be a viable strategy for augmenting neurogenesis of endogenous progenitor cells (Chen *et al.*, 2012).

A large cell-surface carbohydrate, Polysialic Acid (PSA), regulates cell interactions and is harnessed during vertebrate development to promote precursor cell migration and axon path-finding. The induction of PSA expression in damaged adult CNS tissues could help them rebuild by creating conducive conditions for architectural remodeling. This possibility was explored

through two approaches: the regeneration of axons; and the recruitment of endogenous neural precursors to a lesion site. Glial scars that form at CNS injury sites block axon regeneration. It was found that transfection of scar astrocytes by a viral vector encoding polysialyltransferase leads to sustained expression of high levels of PSA. With this treatment, a substantial proportion of severed corticospinal tract axon processes were able to grow through a spinal injury site. Studies of precursor cell migration to a cortical lesion have found that induced PSA expression, in a path extending from the subventricular zone to a lesion near the cortical surface, increased recruitment of BrdU/nestin-positive cells along the path and into the injury site. The displaced precursors were able to differentiate in a regionally appropriate manner. These results suggest that induced PSA expression can be used as a strategy for promoting tissue repair involving both replacement of cells and rebuilding of neural connections (Luo *et al.*, 2011).

1.11. Therapeutic Mechanism-the Three Hypotheses

While initial research has indicated that engraftment and transdifferentiation into neural cells could explain the observed benefit, the exact underlying mechanism of improvement remains controversial. A second hypothesis implicates localized stem/progenitor cell engraftment with subsequent alteration of the loco-regional milieu; however, the limited rate of cell engraftment makes this theory less plausible. There is a growing body of preclinical data supporting the notion that, after intravenous injection, stem/progenitor cells interact with immunologic cells located in organ systems distal to the CNS, thereby altering the systemic immunologic/inflammatory response. Such remote cell “bioreactors” may modulate the observed post-injury pro-inflammatory environment and lead to neuroprotection (Walker *et al.*, 2011).

1.12. Engraftment and Transdifferentiation

Lundberg *et al.* (2009) administered human MSCs into the ipsilateral carotid artery of rats submitted to TBI. The intra-arterial transplantation of MSCs resulted in migration to the lesion and engraftment of the CNS without thromboembolic ischemia.

The Ha laboratory implanted Human Umbilical Cord Blood Mononuclear Cells (HUCBCs) into the injured region and found engrafted HUCBCs up to 8 week after injury. HUCBCs were found to express the neural markers GFAP and Microtubule-Associated Protein 2 (MAP2).

Functional improvement via locomotor testing was observed in the animals for up to 8 week (Calatrava-Ferreras *et al.*, 2012).

The concept of plasticity of stem cells or transdifferentiation could explain the ability of stem cells of one adult tissue to proliferate into different cell lineages (i.e., engraftment of neurons after MSCs therapy) (Li and Chopp, 2009).

The differentiation of MSCs into neural cell lineages *in vitro* uses compounds such as β -mercaptoethanol (Nichols *et al.*, 2013), Dimethyl Sulfoxide (DMSO) (Barnabe *et al.*, 2009), retinoic acid (Jiang *et al.*, 2012) and growth factors FGF and EGF (Aizman *et al.*, 2013). The forming of neurospheres has also been observed, where these are able to produce neurons or astrocytes and oligodendrocytes, visualized by specific immunohistochemical markers (Birenboim *et al.*, 2013).

Although promising studies have shown engraftment and transdifferentiation of progenitor cells transplanted into neural tissue, the importance of engraftment and frequency of transdifferentiation remain extremely controversial in the literature (Zhang and Alexanian 2012), others claim that neural markers may be merely evidencing the result of extreme cellular stress and artifacts of the technique, particularly after the use of aggressive substances such as beta-mercaptoethanol and DMSO (Lu *et al.*, 2004).

1.13. Modulation of the Locoregional Inflammatory Milieu

Progenitor cell migration towards the site of injury and interaction with resident microglia could modulate the locoregional inflammatory response thereby leading to enhanced neuroprotection. The recruitment of inflammatory cells is known to lead to the cascade of secondary damage common to injuries of the Central Nervous System (CNS). Cell activation and infiltration into the injury site is measured by changes in the expression of chemokines (IL-1 alpha, IL-1 beta, IL-6 and TNF alpha), the chemoattractive cytokines. Co-cultures of MSCs with purified immune natural killer-like cells, dendritic cells and both naïve and effector T cells, increase production of anti-inflammatory interleukins IL-4 and IL-10, while reducing the quantity of TNF- α and IFN- γ . Increase in IL-4 together with reduction in IFN- γ promotes a change in the subset of T helper cells, from Th1 cytotoxic cells to Th2 cells. In addition, reduction in TNF- α allied with increase in IL-10 can reduce the maturation of dendritic cells, while increasing the number of regulatory the T cells that

promote an anti-inflammatory or tolerant response (Walker *et al.*, 2010).

Reducing the number of inflammatory cells requested by blocking the action of chemokines has proved a promising approach for reducing neuroinflammation and improving tissue preservation and neovascularization. In addition, several chemokines have been shown to be essential for stem/progenitor cell attraction, survival, differentiation and cytokine production. Thus, chemokines may be indirectly involved in remyelination, revascularization and neuroprotection, important prerequisites for CNS repair after trauma (Jaerve and Mueller, 2012).

Walker *et al.* (2010) implanted MSCs directly into the cortex of rats with TBI and found increased Interleukin 6 (IL-6) in brain tissue supernatant. Subsequently, a series of MSCs *in vitro* and co-cultures of NSCs showed activation of the NSC NF κ B pathway leading to a reduction in cellular apoptosis.

In situations of brain ischemia, trauma or various other pathologies, astrocytes are activated causing a phenomenon called reactive astrogliosis. This process is characterized by hypertrophy, cell proliferation, extension of cell processes, as well as increase in the production of the proteins GFAP, vimentin and nestin (Weber *et al.*, 2013).

Reactive gliosis results in the formation of glial scars. Currently, neural scarring is believed to be responsible for the growth inhibition of neurites, hampering regeneration in the CNS after lesions. In addition, this scarring inhibits communication among existing neuronal processes (Yu *et al.*, 2012).

1.14. Modulation of the Systemic Immunologic Response

Stem cell therapy influences the systemic immunologic response, triggering an increase in anti-inflammatory cytokine and the production of regulatory T-cells, with decreased production of cytotoxic T-cells (Ying *et al.*, 2011). Recently, a study in a rat model of stroke showed that, following stroke, spleen size was reduced concomitantly with CD8+ T-cell counts. The transfusion of systemic HUCBCs in a rat model of stroke showed recovery of spleen weight, splenic CD8+ T-cell counts, as well as extent of brain injury. Moreover, the proliferation of T-cells was reduced commensurate with the increase in IL-10 and a reduction in IFN- γ . The reduced peripheral inflammatory response was associated with a reduction in the volume of the brain infarct by up to 85% (Vendrame *et al.*, 2005).

Theories have also been proposed suggesting that stem cell treatment induces angiogenesis, predominantly responsible for tissue repair (Xiong *et al.*, 2012). In a rat model, intravenous injection of MSCs after induced stroke resulted in augmented levels of endogenous VEGF of the VEGF 2 receptor, as well as increased angiogenesis in the transition zone (Caplan and Dennis, 2006).

It is important to point out that the immune response in the brain is limited and peculiar, a feature afforded by the selective permeability of the blood-brain barrier. However, this is known to be only partially true since in certain situations, infiltration by other cells, especially lymphocytes, can be seen (Sekeljic *et al.*, 2012). In the majority of cases, only the microglia and astrocytes are activated, where these cell types, particularly the former, are responsible for the immunological response in the CNS (Ikeshima-Kataoka *et al.*, 2013).

2. CONCLUSION

Mortality and morbidity of TBI are set to increase globally in coming years. The preclinical work reviewed in this study offers novel data supporting the potential efficacy of cell therapies for TBI. It is now possible to accompany autologous neural stem cells *in vivo* and cell migration, confirming that neural stem cells can selectively target brain injuries and undergo neurogenesis. However, this field is only beginning to understand the complex interplay between neural precursor potential and signalling in their local microenvironment. Although neurogenesis normally occurs in only two areas of the adult brain (SVZ and dentate gyrus), other research suggests that it may be possible to manipulate endogenous neural precursors *in situ* to undergo neurogenesis in other regions of the adult brain. Multipotent precursors capable of differentiating into neurons, astroglia and oligodendroglia exist in many regions of the adult brain. These precursors have considerable plasticity and despite limitations integrating into some areas of the CNS, appear capable of differentiating into neurons appropriate for a wide variety of regions when heterotopically transplanted, or, more recently, recruited *in situ*.

Looking forward, additional preclinical research is warranted to further elucidate the progenitor cell mechanism of action and to aid the planning of quality controlled clinical studies. This holds the key to advancing in the treatment of TBI using stem cell therapy.

2.1. Conflict of Interests

The authors declare that they have no conflict of interest.

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